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FEDERAL DRUG DEVELOPMENT PROGRAMS.(U)
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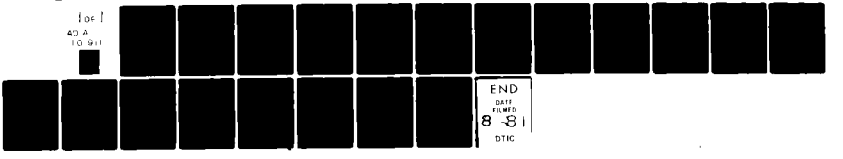

UNITED STATES GENERAL ACCOUNTING OFFICE
WASHINGTON, D.C. 20548

HUMAN RESOURCES
DIVISION

JUL 17 1981

B-202161

The Honorable Henry A. Waxman
Chairman, Subcommittee on Health
and the Environment
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

Subject: Federal Drug Development Programs (HRD-81-125)

This is in response to your request that we develop information on the Federal Government's involvement in drug development programs to assist the Subcommittee in its consideration of the Federal role in developing orphan drugs.

We have had several briefings with your office to discuss information we had obtained during our review. As agreed with your office, this report contains the results of our work as presented during our briefings.

The report is divided into two sections:

--Introduction and scope - includes a discussion of Federal controls over development and marketing of drugs.

--A description of Federal drug development programs - includes 12 programs identified by our study, highlighting the basis for Government involvement, the scope of their activities, the status of drug development in these programs, and some factors to consider in establishing new drug development programs.

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As agreed with your office, we did not obtain written agency comments on this report. However, officials who were responsible for each subject discussed in this report did review a draft pertaining to their respective activities. Their comments have been considered in preparing the final report.

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If you have any questions about the enclosed information, we would be pleased to discuss it with you. As agreed with your office, this report is being made available for general distribution. Also, copies are being sent to the Secretary of Health and Human Services.

Sincerely yours,

Gregory J. Ahart
Director

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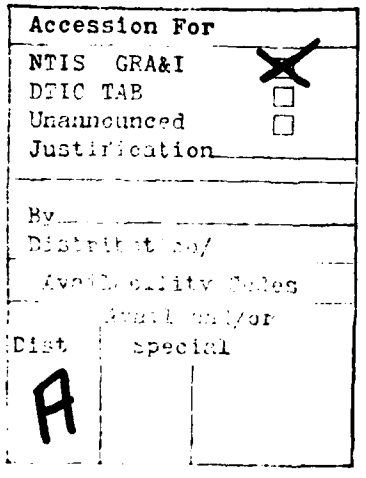

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ABBREVIATIONS

FDA	Food and Drug Administration
FD&C Act	Food, Drug, and Cosmetic Act
HHS	Department of Health and Human Services
IND	investigational new drug
NCI	National Cancer Institute
NDA	new drug application
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OTA	Office of Technology Assessment
PMA	Pharmaceutical Manufacturers Association

INTRODUCTION AND SCOPE

At the request of the Chairman of the Subcommittee on Health and the Environment, House Committee on Energy and Commerce, we made a study to develop information on Federal drug development programs. The Subcommittee wanted to learn about the drug development programs in the National Cancer Institute (NCI) and other institutes at the National Institutes of Health (NIH) as well as programs in other Federal agencies. The Subcommittee was interested in determining whether (1) those programs can serve as models for the development of other drugs and (2) the Federal Government can play a productive role in developing other drugs. These concerns were related specifically to "orphan drugs," a term used to refer to drugs that, for various reasons, are not expected to be developed by industry.

FEDERAL CONTROL OVER DEVELOPMENT AND MARKETING OF DRUGS

The Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 301) provides that a new drug 1/ may not be introduced or delivered for introduction into interstate commerce in the United States unless the Food and Drug Administration (FDA) has approved a new drug application (NDA) for it.

FDA will approve an NDA only if the sponsor of the application shows that the drug is safe and, by substantial evidence, that the drug is effective (for the conditions prescribed, recommended, or suggested in the product's labeling) and is properly manufactured. The FD&C Act states that the standard for substantial evidence is "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved * * * under the conditions of use * * * in the labeling or proposed labeling thereof."

1/A new drug may be an entirely new substance, a marketed drug in a new formulation, or a marketed drug being proposed for a new use for which the drug is not approved.

THE DRUG DEVELOPMENT PROCESS IN GENERAL 1

The process from research to marketing approval of a new drug in the United States takes from 7 to 13 years and costs $30 million to $50 million. The process is usually shorter for generic drugs and for new formulations of an already approved drug. The process involves discovering, testing, and gaining marketing approval for the new chemical. The process is divided into the following three major steps.

--Preclinical research aimed at discovering and identifying a new drug that is sufficiently promising to study in humans.

--Clinical research to determine human efficacy and side effects.

--FDA evaluation and approval of an NDA.

Most preclinical research takes place in industry. With few exceptions, industry's research and decisions in this stage of the process are not regulated directly by FDA. However, FDA's requirements for final approval of an NDA affect the type and direction of research that must be done once a new chemical is identified. The research process starts with a scientific lead to follow concerning a particular disease. The state of knowledge of the disease and the probability of scientific and/or marketing success are evaluated before the research proceeds.

Once a lead is established, chemical compounds are prepared by chemists and are examined in detail by pharmacologists in a broad range of tests (in subcellular cultures and/or laboratory animals). Compounds considered to have the most potential are then subjected to toxicological tests, which usually include determining lethal doses in animals, and pathological studies to detect organ toxicity. Potentially useful compounds are then considered for clinical pharmacology. Compounds chosen for human study must first undergo additional studies to determine how they are metabolized in and excreted from animals. The drug must then be prepared in a form that is stable and usable by the body.

Preclinical research data on the chemistry, pharmacology, and toxicology of the drug is submitted to FDA in a document entitled "Claimed Exemption for an Investigational New Drug (IND)." The

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1/The information in this section was taken from a November 1980 report, "The Food and Drug Administration's Process for Approving New Drugs," prepared by the Subcommittee on Science, Research, and Technology, House Committee on Science and Technology (Ninty-Sixth Congress, Second Session).

FD&C Act states that research on a new drug in human beings can be done only after this notice of claimed exemption for an IND has been submitted to FDA and at least 30 days have expired without notification from FDA that such studies may not commence. The main purpose of the exemption for an IND is to protect the safety of the people on whom the drug is to be tested while developing the data on safety and effectiveness necessary to permit marketing of the drug.

If FDA does not reject the IND, and if the institutions in which the drug will be tested also approve, clinical studies can begin according to three prescribed phases as set forth in FDA regulations.

In phase I of a clinical study, prior to administering the drug to human volunteers for the first time, a pharmacologist must thoroughly study the preclinical data. If more data are required, additional investigations must be made. After satisfactory completion of these studies, the drug is administered to a few volunteers, usually healthy people, but sometimes patients, to ascertain drug metabolism and excretion and estimate the drug's potential for producing adverse effects. These tests usually do not provide data on efficacy of the new drug against the disease it is designed to treat. If sufficient adverse effects are found that would limit the drug's use, the drug will be abandoned at this stage.

If phase I studies show no problems in human toleration, the drug enters phase II of clinical study. In phase II, the drug is studied in patients with the disease which the drug is designed to treat. The objective is to determine whether the drug has the desired therapeutic effect, the dose range at which the effect occurs, and whether any adverse effects will limit the drug's usefulness. Lack of efficacy at this phase will result in abandoning the drug.

Drugs considered to be effective and safe after phase II will enter phase III for more intensive investigation. In phase III, the drug is administered to hundreds and even thousands of patients. The studies are in a clinical setting similar to the environment in which the drug will be used if marketed. Care is taken to detect adverse reactions and potential interactions with other medications. Drugs which are in the various stages of clinical trials are not generally made available to patients outside of these trials. However, FDA has established a "compassionate IND" mechanism whereby these drugs can be made available to patients for which no other therapy is available. The granting of a compassionate IND for a drug is made by FDA on a case-by-case basis.

The clinical and preclinical data on a drug that satisfactorily passes at least two adequate and well-controlled phase III studies are assembled in an NDA and submitted for approval to FDA.

Only about 1 out of every 10 drugs for which a claim for an IND exemption was filed have sufficient merit for filing an NDA.

The NDA must contain all information, both favorable and unfavorable, obtained through the investigations of the safety and effectiveness of the new drug. It must also contain information on the process for making the drug and how the quality of the drug will be assured. Each NDA consists of from 2 to 15 volumes of summary material accompanied by about 10 to 100 volumes (sometimes up to 400 volumes containing 100,000 to 200,000 pages) of raw data.

Under the FD&C Act, FDA has 180 days to review and approve or disapprove an NDA. FDA must determine whether the drug (1) is safe and effective; (2) can be manufactured consistently; and (3) will, when used properly, result in benefits that outweigh its risks. FDA must also approve the description of the drug to be distributed to prescribing physicians.

FDA's process for approving NDAs was the subject of our report entitled "FDA Drug Approval--A Lengthy Process That Delays the Availability of Important New Drugs" (May 28, 1980, HRD-80-64).

NIH AND OTHER AGENCY INVOLVEMENT IN THE DRUG DEVELOPMENT PROCESS

Although most preclinical and clinical studies to develop and market new drugs are conducted by industry, NIH and to a much lesser extent the Department of the Army and the National Institute on Drug Abuse (NIDA) have established programs to conduct such studies. Seven NIH institutes operate a total of 10 drug development programs, and Army and NIDA each operate one. The table on the following page shows the program areas, when the programs were started, their estimated funding levels, and the number of new drugs developed as a result of the programs.

ENCLOSURE I

ENCLOSURE I

Program area	Administering agency (note a)	Year started	Estimated fiscal year 1980 funding (note b)	Number of drugs developed (note c)
			(millions)	
Cancer	National Cancer Institute	1955	$40.0	21
Malaria/tropical diseases	Walter Reed Army Institute of Research	1963	4.6	8
Vaccines	National Institute of Allergy and Infectious Diseases	1965	9.4	2
Epilepsy	National Institute of Neurological and Communicative Disorders and Stroke	1968	1.6	3
Antivirals	National Institute of Allergy and Infectious Diseases	1969	1.2	1
Contraceptives	National Institute of Child Health and Human Development	1971	6.7	0
Caries (tooth decay)	National Institute of Dental Research	1971	0.6	0
Sickle cell anemia	National Heart, Lung, and Blood Institute	1972	0.2	0
Narcotic abuse treatment	National Institute on Drug Abuse	1972	2.4	0
Cooley's anemia	National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases	1973	0.2	0
Blood substitutes	National Heart, Lung, and Blood Institute	1974	0.3	0
Biological response modifiers	National Cancer Institute	1979	13.0	0
Total			$79.6	35

a/The Walter Reed Army Institute of Research is a part of the Department of the Army. NIDA is in the Alcohol, Drug Abuse, and Mental Health Administration of the Department of Health and Human Services (HHS). All other institutes listed are in NIH.

b/These estimates include funds for research contracts and intramural research directly related to drug development.

c/Except for the eight drugs developed under the malaria/tropical disease program, these are the numbers of drugs developed under the programs and approved as NDAs. The eight malaria/tropical disease drugs are not covered by approved NDAs, but were made available under the program. Also, 10 cancer drugs (in addition to the 21 included here) were substantially developed before the cancer drug program began.

STUDY SCOPE AND METHODOLOGY

Our study was directed toward identifying and describing the drug development programs at NIH and other Federal agencies. We did not evaluate the quality of the programs or their accomplishments.

We made our study during 1980 and 1981 at NIH in Bethesda, Maryland. Through discussions with NIH officials, we learned that, in addition to 10 programs, conducted by seven NIH institutes, the Walter Reed Army Institute of Research (Washington, D.C.), and HHS' NIDA (Rockville, Maryland) were involved in drug development programs.

We interviewed officials representing each of the 12 programs and reviewed reports and records relating to the programs. Because of the relative size of NCI's cancer drug program and the Subcommittee's interest, we devoted most of our effort to that program.

We interviewed FDA officials in Rockville, Maryland, and reviewed FDA records and reports concerning FDA's drug approval process and FDA's involvement in two studies of the orphan drug issue. We also interviewed representatives of the Pharmaceutical Manufacturers Association (PMA), the American Cancer Society, and several private drug companies involved in cancer drug development.

DESCRIPTION OF FEDERAL DRUG DEVELOPMENT PROGRAMS

To aid the Subcommittee in its study of the drug development process and programs, we assembled the data we obtained into segments to answer the following questions:

--Why were the programs started?

--How are new drugs identified, acquired, and screened for development?

--How are the agencies involved in drug development?

--What is the status of drugs being developed?

--What are some factors to consider in establishing a new drug development program?

WHY THE PROGRAMS WERE STARTED

The 12 Federal drug development programs were initiated because of perceived needs for attention to a specific disease or problem and a belief that industry could not be expected to fill these needs. Industry's reluctance is attributed by the agencies to the uncertain profitability of developing and marketing new drugs, as indicated by the probable size of the market in relation to development and marketing costs.

Although none of the 12 drug development programs were specifically mandated by legislation, 5 of the programs began in response to broader legislative mandates to do research on causes of and treatments for specific diseases or to directions from congressional committees to do such research. The other seven programs were started by the administering agencies without such specific expressions of congressional interest.

Cancer program

NCI's anticancer drug development program began when the Congress provided $5 million for that purpose in 1955. This was prompted mainly by the discovery that two chemicals--nitrogen mustard and methotrexate--were effective in treating leukemia and some lymphomas. Also, according to a 1957 NCI report to the Congress, industry activity in anticancer drug development had been intermittent because (1) most pharmaceutical firms considered anticancer drug development to be a risky, low return investment; (2) testing methods were expensive, slow, and uncertain; (3) clinical trials were difficult to conduct; and (4) industry believed that any new anticancer drugs would become part of the public domain, which would limit the opportunity to recover costs or make a profit.

Other programs

The bases for starting the 11 other drug development programs were as follows.

The Department of the Army initiated the malaria/tropical diseases program in 1963 in response to the need to protect military personnel from such diseases in areas where the diseases were not responsive to existing drugs. An official told us that (1) when the program was started, industry was doing little work in the area of tropical diseases, (2) an informal survey by the Army at that time showed that drug companies' interest in the area was nonexistent or declining, and (3) between 1961 and 1981, private industry developed and marketed only one antimalarial drug (a combination of two older drugs), which has never been approved for marketing in the United States.

The vaccine program, which is for testing and developing vaccines primarily for viruses was begun in 1965 by the National Institute of Allergy and Infectious Diseases following a recommendation by that Institute's advisory committee. 1/ In discussing the basis for this program, a program official provided a 1979 report by the Office of Technology Assessment (OTA) which states that (1) during the past few decades the number of manufacturers of vaccines in the United States has been declining, (2) the number of such manufacturers decreased from 37 to 18 from 1967 to 1979, and (3) several factors have influenced the maufacturers' decisions on whether to develop and market new vaccines. The influential factors cited by the OTA report included a relatively small market, low profits, high capital investment requirements, extensive Federal regulations, and unpredictable vaccine liability risks.

The epilepsy drug development program was established in 1968, which was about 2 years after an epilepsy section was established in the National Institute of Neurological and Communicative Disorders and Stroke. The epilepsy section had been established by the Secretary of HHS because of the need to stimulate and support research and development of antiepilepsy drugs by industry. Program officials told us that about 25 percent or more of the Nation's 2 million epileptics are not adequately responsive to existing treatments. Between 1938 and 1960, 13 epileptic drugs were marketed. No additional new drugs were marketed in the United States before the Federal program was started. According to program officials, several new drugs were made available in Europe,

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1/NIH has several advisory committees that make recommendations to the various institutes concerning program directions. These committees consist of representatives from science and research who are considered to be experts in the institutes' program areas.

but industry stopped developing such drugs for use in the United States because of difficulties in meeting the safety and effectiveness requirements of the FD&C Act.

The antiviral drug development program was started in 1969 by the National Institute of Allergy and Infectious Diseases in response to a recommendation of its Vaccine Development Advisory Committee. Program officials told us that, at the start of the program, (1) no successful antivirals were available and (2) although interferon (the first identified antiviral substance) had been discovered in 1959, no one was developing it as an antiviral. The advisory committee believed that not only should the Institute study interferon, but it should also determine if antivirals in general were useful.

The contraceptive development program was created in 1971 as part of the National Institute of Child Health and Human Development on the recommendation of an advisory council within the Institute. Although industry had been involved in research in the 1950s and early 1960s, the FDA drug development regulations and the increasing costs of development caused industry to lose interest. The last drug introduced by industry was marketed in the late 1960s.

The caries (tooth decay) drug development program was started in 1971 by the National Institute of Dental Research in response to a presidential directive. Although caries affects or will affect 95 percent of the population, a program official stated that industry has been reluctant to develop drugs in this area because of the costs of extensive testing that would be required to obtain FDA approval. Because such drugs would be for use by otherwise healthy people, evidence of the drug's safety would have to be more extensive than that required for drugs for debilitating diseases.

The sickle cell anemia drug development program was started in 1972 by the National Heart, Lung, and Blood Institute in response to the National Sickle Cell Anemia Control Act. Program officials told us that, at that time, no drugs were available for treating the disease and industry was doing nothing to develop such drugs because of the small market (about 50,000 people).

The narcotic abuse drug development program is conducted by NIDA as part of its implementation of the Drug Abuse Office and Treatment Act of 1972 (21 U.S.C. 1101). At the start of the program only one drug--methadone--had been approved by FDA for treating narcotic addiction. A NIDA official told us that the pharmaceutical companies are reluctant to develop such drugs because of the possible stigma that might result from such activities.

ENCLOSURE II

The drug development program for Cooley's anemia was started in 1973 by the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. This was in response to the National Cooley's Anemia Control Act of 1972, which increased emphasis on research related to the disease. Cooley's anemia is an inherited blood disorder found most commonly in people of Mediterranean descent. About 1,000 people in the United States have this disease, which requires blood transfusions throughout one's life. One drug--desferrioxamine--was developed and approved before the program was started, but this drug is not widely used because it is painful, expensive, and requires daily dosage. A program official told us that drug companies are not interested in developing drugs in this area because the market is too small.

The blood substitutes development program was established by the National Heart, Lung, and Blood Institute in 1974 because prior research indicated that certain chemical solutions--called perfluorochemicals--might be usable as blood substitutes. A program official stated that such drugs could be useful in situations that preclude transfusions. Only one drug company has developed such a blood substitute, and as of June 1981, that drug was in clinical trials. The program official said that this was the only drug company involved in developing perfluorochemicals for medical use.

The biological response modifiers program was started by NCI in 1979 as a special effort to develop interferon and other biological agents with potential for controlling the growth of cancer cells. The Senate Committee on Appropriations directed that NCI use a substantial portion of its fiscal year 1980 budget increase to develop interferon and other biological agents. This program was established separately from the existing anticancer drug program because NCI believed that biological response modifiers warranted systematic developmental efforts.

HOW NEW DRUGS ARE IDENTIFIED, ACQUIRED, AND SCREENED FOR DEVELOPMENT

The first steps in the drug development process are to identify, acquire, and screen new drugs that have potential for treating the disease involved. Generally, the institutes administering the 12 programs we studied had adopted similar methods of identifying and acquiring new drugs. Also, each program involved some form of screening to promptly eliminate drugs with little or no potential. The programs varied significantly, however, in terms of the numbers of drugs acquired and screened.

Under six programs in which the question of the proprietary interests of the drugs' suppliers became a factor, the institutes made arrangements to give the suppliers exclusive rights to the data developed under the programs.

Identifying and acquiring new drugs

Under the 12 programs, new drugs are identified and acquired by maintaining contact with scientists in industry and research institutions, reviewing research literature, synthesizing existing drugs, and/or experimenting with natural products. Such activities are carried out by institute personnel or under contract. Drugs acquired from outside sources are either purchased or received at no cost.

Under its anticancer drug program, NCI has identified and acquired about 340,000 compounds for screening. Most of the chemicals were acquired by soliciting submissions from outside sources. These compounds were identified mainly through organized reviews of medical and scientific journals and chemical supply company catalogs. Less than 10 percent of the compounds were developed through NCI-supported experiments.

To encourage industry to submit chemicals for the program, NCI adopted a policy in 1956 under which suppliers of (1) patented chemicals were allowed to retain their patent rights and exclusive rights to data developed under the program and (2) unpatented drugs were given exclusive rights to the data developed.

Under the 11 other programs, a combined total of about 288,000 chemicals, including about 280,000 for the malaria program, were acquired for screening. These were identified and acquired in much the same way as the anticancer drugs. In five of these programs--malaria, epilepsy, contraceptives, caries, and Cooley's anemia--the institutes adopted arrangements similar to those adopted by NCI to protect the proprietary interests of the suppliers of the drugs.

Screening new drugs for further development

The screening process involves testing a new drug in animals and/or in laboratory cultures to see if it is active against a disease. If it is active, the drug is submitted for further preclinical studies as prescribed by FDA regulations.

Under the anticancer drug program, NCI initially established a mass screening program: all available compounds were acquired and screened with little or no prior knowledge of the drugs' anticancer properties. Partly because of criticism of this practice from the scientific community, NCI adopted a practice in 1975 under which fewer compounds were screened and inactive compounds were eliminated earlier in the process. This resulted in reducing the number of compounds screened from about 40,000 to 15,000 a year. Under NCI's revised process, all compounds of interest are subjected to a preliminary screen against a single type of tumor in

ENCLOSURE II

mice. Of the 15,000 compounds subjected to this preliminary screen each year, less than 500 are shown to be active and are subjected to further testing.

The additional testing involves a series of different types of human and animal tumors transplanted in mice. A positive reaction in any one of these tumors is sufficient evidence for NCI to pursue the drug further. All screening data are collected and reported to NCI's Decision Network Committee. This committee is made up of 30 NCI staff members including intramural laborabory scientists and clinical investigators. It recommends to the director of the Division of Cancer Treatment which drugs should be considered further. If the division director agrees with the committee's recommendation that a drug be further developed, feasibility studies for large scale production and formulation are initiated. These are to facilitate production of the drug for both toxicology studies and clinical trials. An affirmative decision by the director to move a drug forward commits large amounts of the division's resources to the next stage of the drug's development.

The screening processes under the 11 other drug development programs have not involved nearly as many drugs as the cancer program. With the exception of the malaria, epilepsy, and contraceptives programs, these programs have not involved broad searches and screening of new drugs. As of 1981 the total numbers of drugs screened under the 11 programs are as follows.

Programs	Estimated number of drugs screened
Malaria/tropical diseases	280,000
Vaccines	60
Epilepsy	4,400
Antivirals	50
Contraceptives	2,800
Caries (tooth decay)	300
Sickle cell anemia	25
Narcotic abuse treatment	6
Cooley's anemia	150
Blood substitutes	80
Biological response modifiers	a/not applicable

a/Screening program is in planning stage.

Most of the screening of new drugs under the cancer program and the 11 other programs is done by contractors. In some cases, screening is not needed because sufficient data have already been developed before the drug was acquired for further development.

HOW THE AGENCIES ARE INVOVLED IN DRUG DEVELOPMENT

By law, a new drug cannot be marketed unless FDA finds that it is safe and, based on substantial evidence, that it is effective for the use intended. (See p. 1.) The preclinical and clinical stages of drug development under the 12 programs we studied were designed to at least satisfy the requirements of the law and FDA regulations.

NIH's seven institutes and the two other institutes with drug development programs perform or sponsor the preclinical and clinical studies needed to develop the scientific evidence to support the safety and effectiveness of the new drugs. The degree of involvement by the institutes in each stage of development may vary for different drugs, depending on the extent that private industry will participate. In most cases, the institutes' involvement in getting a new drug approved ends when clinical studies are completed.

With some exceptions, the evidence obtained in the screening and the preclinical and clinical studies is turned over to a private company for use in obtaining an approved NDA from FDA. The company may or may not have participated in the various stages of the development process. Upon NDA approval, the company may market the new drug.

STATUS OF DRUGS BEING DEVELOPED

The 12 programs have resulted in the screening of many thousands of drugs and in detailed preclinical and clinical studies of several hundred of those drugs. About 400 drugs have entered the clinical trial stage under IND applications approved by FDA. At the time of our review, 35 new drugs had been developed under the programs (see p. 5). A total of 102 drugs were still being studied under approved INDs or were being considered by FDA for approval as NDAs. Of those drugs, 72 were anticancer drugs, 13 were malaria drugs, 6 were vaccines, 4 were antivirals, 3 were contraceptives, 3 were narcotic abuse drugs, and 1 was for sickle cell anemia.

SOME FACTORS TO CONSIDER IN ESTABLISHING NEW DRUG DEVELOPMENT PROGRAMS

The 12 existing drug development programs were started because of perceived needs for attention on a specific disease or problem and a belief that industry could not be expected to fill these needs. Other factors that NIH or FDA officials believe should be considered in connection with the need for and feasibility of new drug development programs are as follows:

--The absence of an overall strategy for dealing with the issue of "orphan drugs," or drugs that industry has little or no interest in developing.

--The number of diseases for which no adequate drugs and/or laboratory models for testing drugs have been developed.

Orphan drugs

FDA has coordinated two interagency studies--one beginning in 1973 and one in 1978--of the orphan drug issue and what the Government's role should be concerning such drugs. At the time of our review, no firm decision had been made on this issue.

The 1973 study committee consisted of 5 individuals from FDA, 11 from NIH, 2 from the Alcohol, Drug Abuse, and Mental Health Administration, and 1 each from the Center for Disease Control, the National Bureau of Standards, and the George Washington Medical Center. The committee's May 1975 report noted that the medical community, Public Health Service officials, and some drug firms had been concerned that drugs with potential therapeutic value were not being developed and marketed. The report said that this was apparently because the anticipated sales volume of such drugs was too low to compensate firms for the costs of developing the drugs, obtaining FDA approval, and producing and marketing the drugs.

The committee was divided into six study groups, each to report on a segment of the overall problem, as follows:

--Study Group I was to define the orphan drug problem, its scope, and its importance in terms of public health.

--Study Group II was to consider economic incentives to firms to develop orphan drugs.

--Study Group III was to consider the need for a Government organization for drug development and distribution.

--Study Group IV was to cover the legalities regarding whether a drug company can be given exclusive rights to data developed by the Government.

--Study Group V was to study the feasibility of liability insurance for clinical testing.

--Study Group VI was to cover problems of orphan drugs of foreign origin or ownership.

Study Group I defined an orphan drug as a drug that is considered not to be sufficiently profitable for a firm to develop, produce, and market even though the drug might be more effective in some patients than existing treatment.

The study group, however, was unable to say whether the orphan drug problem was significant enough to be considered a public health problem. The study identified the following obstacles to developing a complete list of orphan drugs:

--Many of the drugs on earlier lists may no longer be classified as orphan drugs or may have been displaced by drugs with better potential use.

--Knowledge of the drugs tends to be limited and not widespread.

--Clinical investigators may not be able to accurately assess the commercial value of drugs with which they are working. Therefore, their identification of a drug as an orphan drug may not be reliable.

Because of these obstacles, the study committee believed that the development of a complete list would require consulting with marketing experts and with investigators throughout the Government, industry, and academic institutions. Efforts to develop such a list were not undertaken.

Study Group II identified several economic incentives to encourage more drug firms to provide better data on orphan drugs and develop such drugs. The group recognized the difficulty in determining which drugs should be classified as orphan drugs and concluded that further study was needed to better understand the magnitude of the problem.

The inability of Study Group I to define the scope of the problem also hindered the work of Study Group III in determining what action should be taken by the Government. Members of Study Group III could not agree on the advisability of establishing a Government unit to promote the development and marketing of such drugs. The group recommended only that Government organizations exchange information on their attempts to promote such drugs.

Study Group IV, in considering the issue of giving drug companies exclusive rights to Government data, noted that patent law was being interpreted by the courts to mean that an exclusive license could not be granted and that additional study of the patent issue may be desirable.

Study Group V found that drug firms' liability insurance generally does not cover patients' claims arising from adverse effects before the drug is approved.

Concerning orphan drugs of foreign origin, Study Group VI concluded that no specific action should be taken. The group believed that a study should be made on the feasibility of a Government or private logistics and/or supply center for both foreign and domestic orphan drugs.

ENCLOSURE II

In its 1975 report to the Assistant Secretary for Health, the committee concluded that there was not enough information on the extent of the orphan drug problem to support overall policy recommendations. The committee recommended that:

--A thorough study be made of the orphan drug problem.

--Lists of drugs in this category, their uses, and the potential market for them be made available to investigators, drug firms, and physicians.

--A clear statement be made by FDA on its policy allowing certain deviations from normal procedures for obtaining approval of these drugs.

--Information about drugs and sponsors for which IND studies have been discontinued because of lack of commercial interest, including data on clinical trials for toxicity, be provided to investigators, drug firms, and physicians.

In response to the committee's report, the Assistant Secretary told FDA that the study was of interest and that FDA should continue to look into this area.

In March 1978, FDA formed an interagency task force to propose actions for dealing with orphan drugs. The task force included most of the members of the previous committee and other HHS officials, FDA advisory committee members, private consultants, and pharmaceutical industry representatives.

The task force report, issued in June 1979 to the Secretary of HHS, stated that the orphan drug problem was well substantiated and that it was not necessary to document the extent of the problem. The report contained several recommendations to provide incentives for industry to develop and market drugs. As of May 1981, no official response had been made to the report. An FDA official stated in March 1981 that although the report was not acted upon formally, it has served as the basis for further discussion.

An FDA official told us in May 1981 that because only a few new orphan drugs are identified each year, and in view of proposed actions by PMA, the action recommended by the task force may not be needed. PMA has proposed to form a commission on "drugs for rare diseases" to collect and disseminate research information on such drugs. The FDA official said that something else may still be needed to deal with the few new orphan drugs as they are identified.

Diseases for which no adequate drugs or testing models are available

According to NIH officials, there are many hundreds of diseases for which there are no known cures. Many of these diseases are considered to be of low incidence; some are rare. Because of their low incidence, little is known about these diseases and little research is being done on them. Also, for many of them, no model for testing drugs or other forms of treatment has been developed.

For example, officials in the National Institute of Neurological and Communicative Disorders, and Stroke told us that in the area of neurology alone

--there are at least 280 diseases,

--about 165 of the 280 diseases each afflict 3,000 people or fewer and about 75 of these afflict 30 people or fewer,

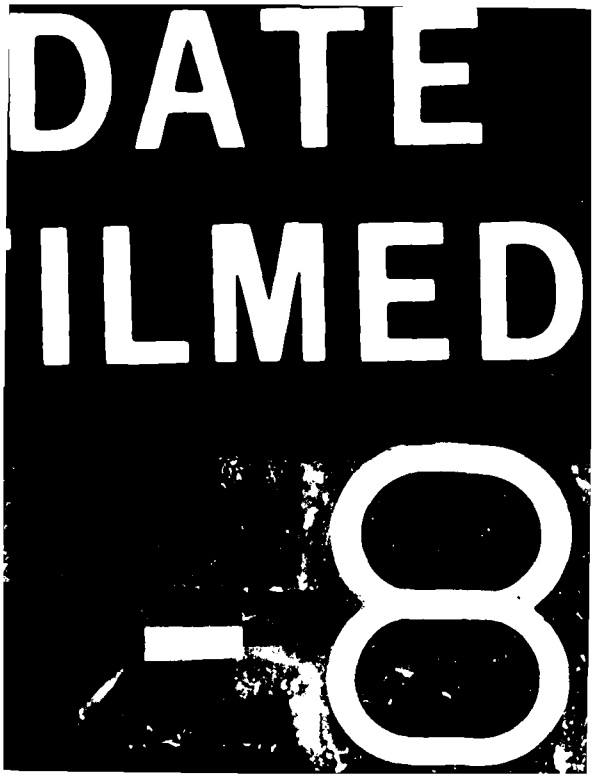
--no drugs are available for at least half of the 280 diseases,

--no models have been developed for testing the effects of drugs on the diseases for at least 20 percent of the 280 diseases, and

--neither a drug nor a model for testing was available for at least 40 of the diseases.

According to NIH researchers, the toxicity of a compound can be determined without a model for the disease but drug efficacy in humans cannot. A model for a disease is an imperfect representation of the disease. The better the model, the more closely it represents the disease in humans.

According to NIH officials, it is possible to research a disease without a model, but the only way to determine efficacy would be to test drugs directly in humans. Therefore, without a model, mass screening of drugs would not be feasible.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